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GE HEALTHCARE BIO-SCIENCES CORP.
PATENT DEPARTMENT
101 CARNEGIE CENTER
PRINCETON, NJ 08540

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POHNERT, STEVEN C	

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melissa.leck@ge.com

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ANUP SOOD, SHIV KUMAR, JOHN NELSON, and CARL FULLER

Appeal 2009-003262
Application 10/773,000
Technology Center 1600

Decided: April 14, 2010

Before ERIC GRIMES, DONALD E. ADAMS, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 1-56, the only claims pending in this application. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

The claims are directed to a method of sequencing a target region of a nucleic acid template. Claims 1 and 32 are illustrative:

1. A method of sequencing a target region of a nucleic acid template, comprising:

a) conducting a nucleic acid polymerization reaction on a solid support, by forming a reaction mixture, said reaction mixture including a nucleic acid template, a primer, a nucleic acid polymerizing enzyme, and one terminal-phosphate-labeled nucleoside polyphosphate which is substantially non-reactive to phosphatase, said nucleoside polyphosphate is selected from a nucleoside with a natural base or a base analog

wherein a component of said reaction mixture or complex of two or more of said components, is immobilized on said solid support, and said component or components are selected from the group consisting of said nucleic acid template, said primer, and said nucleic acid polymerizing enzyme,

and

said reaction results in production of labeled polyphosphate if said terminal-phosphate-labeled nucleoside polyphosphate contains a base complementary to the template base at the site of polymerization;

b) subjecting said reaction mixture to a phosphatase treatment to produce a detectable species if said labeled polyphosphate is produced in step a);

c) detecting said detectable species without first separating by charge of said detectable species from the reaction mixture;

d) continuing said polymerization reaction by adding a different terminal-phosphate-labeled nucleoside polyphosphate selected from the remaining natural bases or base analogs to said reaction mixture and repeating steps b and c; and

e) identifying said target region sequence from the identity and order of addition of terminal-phosphate labeled nucleoside polyphosphates resulting in production of said detectable species.

32. A method of sequencing a target region of a nucleic acid template, comprising:

a) conducting a nucleic acid polymerization reaction on a solid support, by forming a reaction mixture, said reaction mixture including a nucleic acid template, a primer, a nucleic acid polymerizing enzyme, and one terminal-phosphate-labeled nucleoside polyphosphate with 4 or more phosphates which nucleoside polyphosphate is substantially non-reactive to phosphatase, and said nucleoside polyphosphate is selected from a nucleoside with a natural base or a base analog and

wherein a component of said reaction mixture or a complex of two or more of said components, is immobilized on said solid support, and said component or components are selected from the group consisting of said nucleic acid template, said primer, and said nucleic acid polymerizing enzyme,

and

said reaction results in production of labeled polyphosphate if said terminal-phosphate-labeled nucleoside polyphosphate contains a base complementary to the template base at the site of polymerization;

b) detecting said labeled polyphosphate without first separating by charge of said labeled polyphosphate from the reaction mixture;

c) continuing said polymerization reaction by adding a different terminal-phosphate-labeled nucleoside polyphosphate selected from the remaining natural bases or base analogs to said reaction mixture and repeating step b; and

d) identifying said target region sequence from the identity and order of addition of terminal-phosphate labeled nucleoside polyphosphates resulting in production of said labeled polyphosphates.

The Examiner relies on the following evidence:

Bronstein et al.	US 5,112,960	May 12, 1992
Keller et al.	US 5,656,462	Aug. 12, 1997
Lichtenwalter	US 5,683,875	Nov. 4, 1997
Hattori et al.	US 5,821,095	Oct. 13, 1998
Williams et al.	WO 01/94609 A1	Dec. 13, 2001
Wittwer et al.	US 6,174,670 B1	Jan. 16, 2001

The rejections presented by the Examiner follow:

1. Claims 1-56 stand rejected under the written description provision of 35 U.S.C. § 112, first paragraph.

2. Claims 1-7, 9, 11-18, 20-23, 27-38, 40, 42-45, and 47-56 stand rejected under 35 U.S.C § 102(b) as being anticipated by Williams[1].

3. Claims 8 and 39 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Williams and Wittwer.

4. Claims 10 and 41 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Williams and Keller.

5. Claims 19 and 46 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Williams and Lichtenwalter.

6. Claims 23-25 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Williams and Hattori.

7. Claims 25 and 26 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Williams and Bronstein.

We reverse the rejection under 35 U.S.C. § 112, first paragraph. We affirm all other grounds of rejection.

Written Description:

ISSUE

Did the Examiner err in concluding that Appellants' Specification does not provide written descriptive support for the detection of detectable

[1] The Examiner did not include claims 48 and 51-54 in the statement of the rejection (Ans. 4). Nevertheless, the Examiner addressed these claims in the body of the rejection (*see* Ans. 11-12 and Fin. Rej. 11-12). Accordingly, we find the Examiner's failure to include claims 48 and 51-54 in the statement of the rejection to be a harmless typographical error.

species/labeled polyphosphate without first separating the detectable species/ labeled polyphosphate from the reaction mixture by charge?

FINDINGS OF FACT

FF 1. The Examiner finds that Appellants' "specification does not provide [a] basis for detection without separation based on charge" (Ans. 4).

FF 2. Appellants disclose that

> The methods provided by this invention utilize a nucleoside polyphosphate, . . . with an electrochemical label, mass tag, or a colorimetric dye, a chemiluminescent label, or a fluorescent label attached to the terminal-phosphate. When a nucleic acid polymerase uses this analogue as a substrate, an enzyme-activatable label would be present on the inorganic polyphosphate by-product of phosphoryl transfer. Cleavage of the polyphosphate product of phosphoryl transfer via phosphatase, leads to a detectable change in the label attached thereon.

(Spec. 11: 10-18.)

FF 3. Appellants disclose an alternative, wherein "it is possible to physically separate the labeled polyphosphate product by chromatographic separation methods before identification by fluorescence, color, chemiluminescence, or electrochemical detection" (Spec. 13: 32 - 14: 2).

PRINCIPLES OF LAW

Under the written description requirement of 35 U.S.C. § 112, first paragraph, "the [A]pplicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). "In order to satisfy the written description requirement, the

disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue." *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000).

ANALYSIS

The Examiner finds that Appellants' "specification does not provide [a] basis for detection without separation based on charge" (FF 1). Appellants contend that when their Specification is read as a whole it "describes sequencing methods which do not require a separation step, prior to the detecting step, of either the detectable species or the labeled polyphosphate from the reaction mixture" (App. Br. 5). We agree (FF 2-3). It is evident from the examples that the detection of the label occurs without chromatographic separation. While Appellants also disclose the use of chromatographic separation methods (*e.g.,* separation by charge) prior to detection, Appellants make clear that this is an alternative method to detection without chromatographic separation (FF 3).

CONCLUSION OF LAW

The Examiner erred in concluding that Appellants' Specification does not provide written descriptive support for the detection of detectable species/labeled polyphosphate without first separating the detectable species/ labeled polyphosphate from the reaction mixture by charge. The rejection of claims 1-56 under the written description provision of 35 U.S.C. § 112, first paragraph is reversed.

Anticipation:

ISSUE

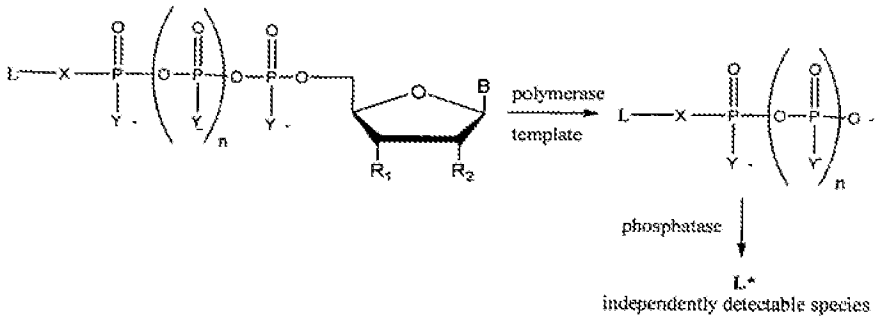
Does the evidence of record support the Examiner's finding that Williams anticipates Appellants' claimed invention?

FINDINGS OF FACT

FF 4. The Examiner finds that Williams teaches a method wherein a "detectable moiety is released as a charged detectable moiety when the NP [(nucleotide phosphate)] is incorporated into the primer nucleic acid" (Ans. 5).

FF 5. The Examiner finds that Williams teaches that "[u]pon incorporation by a polymerase, the dNTP is hydrolyzed as usual and the liberated pyrophosphate-dye moiety diffuses into the surrounding medium. The free dye molecule is fluorescent and its appearance is imaged at video-rate under a microscope . . . (page 22, lines 31 to top of page 23)" (Ans. 27). Therefore the Examiner finds that "Williams teaches detection without separation by charge" (Ans. 28).

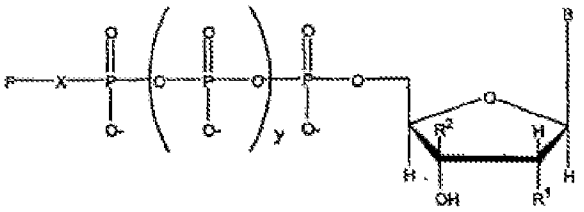
FF 6. The reaction scheme encompassed by the claims is disclosed on page 11 of Appellants' Specification is reproduced below:



(Spec. 11: 24-25.) Appellants disclose that the foregoing scheme "shows the most relevant molecules in the methods of this invention; namely the terminal-phosphate-labeled nucleotide, the labeled polyphosphate by-product and the enzyme-activated label" (Spec. 11: 21-23).

FF 7. Appellants disclose that the label (L) "is a phosphatase activatable label which may be a chromogenic, fluorogenic, chemiluminescent molecule, mass tag or electrochemical tag" (Spec. 12: 1-3).

FF 8. Williams teaches "charge-switch nucleotide phosphate probes" of the following formula:



I

(Williams 15: 1-2.) "In Formula I, F is a fluorophore or dye" (Williams 15: 22).

FF 9. Williams teaches that "[m]any dyes or labels are suitable for charge-switch nucleotide phosphates of the present invention" including "fluorescent and chromogenic molecules" (Williams 16: 2-4).

FF 10. Appellants disclose a method wherein reagents are incubated

> [I]n the presence of a nucleic acid polymerizing enzyme, a phosphatase and a terminal-phosphate-labeled nucleoside polyphosphate, which reaction produces labeled polyphosphate if the nucleotide present is complementary to the target sequence at the site of polymerization. *The labeled polyphosphate then reacts with phosphatase* or a phosphate or polyphosphate transferring enzyme *to produce free label with a signal readily distinguishable from the phosphate bound dye*.

(Spec. 4: 3-9 (emphasis added).)

FF 11. Williams teaches "the use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the [phosphate detectable moiety,] PPi-F[2]" (Williams 25: 12-13).

FF 12. Appellants disclose that "while RNA and DNA polymerases are able to recognize nucleotides with modified terminal phosphoryl groups, the inventors have determined that this starting material is not a template for phosphatases" (Spec. 11: 18-21).

FF 13. "In certain aspects [of Williams' invention], a change in charge sign . . . is utilized to separate the γ -dNTP-Dye from the PPi-Dye" (Williams 21: 18-19).

FF 14. Williams also teaches that "[u]pon incorporation by a polymerase, the dNTP is hydrolyzed as usual and the liberated pyrophosphate-dye moiety diffuses into the surrounding medium. The free dye molecule is fluorescent and its appearance is imaged at video-rate under a microscope. A flowing stream sweeps the dye away from the parent DNA molecule" (Williams 22: 31-34).

FF 15. Williams teaches *another embodiment*, wherein an intact NP probe is separated from a phosphate detectable moiety, which comprises "*applying an electric field to the sample stream*, thereby separating the labeled NP from the charged detectable moiety" (Williams 22: 3-4 (emphasis added)).

PRINCIPLES OF LAW

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior

[2] Williams defines "F" as "a fluorophore or dye" (Williams 15: 22).

art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

ANALYSIS

Appellants provide separate arguments for the following groups of claims: (I) claims 1-7, 9, 11-18, 20-23, 27-31 and (II) claims 32-38, 40, 42-45, and 47-56. Claims 1 and 32 are representative. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Claim 1:

Appellants contend that while Williams "suggests the use of a phosphatase to enhance the charge-switch magnitude of the labeled polyphosphate, the property/detectability of the label in Williams et al. remains the same before and after the phosphatase treatment" (App. Br. 6-7). Accordingly, Appellants contend that "[t]he only change phosphatase treatment brings to the label in Williams et al. is a change in charge" (App. Br. 7; *see also* FF 11).

In contrast, Appellants contend that their claim 1 requires the phosphatase treatment "to generate a detectable species" (App. Br. 6).

We are not persuaded. Appellants' claims and Williams both use a terminal-phosphate-labeled nucleotide (FF 6 and 8). Appellants' claims and Williams both teach the use of a chromagenic or fluorogenic label (FF 7 and 9). We recognize the requirement in Appellants' claim 1 that the terminal-phosphate-labeled nucleoside polyphosphate "is substantially non-reactive to phosphatase" (Claim 1). In that regard, we recognize Appellants' disclosure that they "have determined that . . . [the terminal-phosphate-labeled

nucleotide] is not a template for phosphatases" (FF 12). This is, however, a property of the terminal-phosphate-labeled nucleotide. Therefore, Williams' terminal-phosphate-labeled nucleotide, which appears to be identical, would also not be a template for phosphatases. Appellants have not provided persuasive argument or evidence on this record to support a conclusion that their terminal-phosphate-labeled nucleotide is different from that taught by Williams.

Appellants and Williams both treat the by-product of the polymerase reaction with a phosphatase (FF 6 and 11). Appellants have failed to establish that the product resulting from their phosphatase treatment differs from the product obtained by Williams' phosphatase treatment.

We recognize Appellants' contention that "[w]ithout physical separation, it is impossible to distinguish the reaction product [of Williams' method] from the dye-labeled nucleotide" (App. Br. 7). We are not persuaded. As discussed above, Appellants have failed to establish a structural difference between the reaction products of their claim 1 and those taught by Williams. We recognize Appellants' disclosure that phosphatase treatment produces *"free label with a signal readily distinguishable from the phosphate bound dye*" (FF 10), However, absent evidence to the contrary, it would appear that if Appellants' detectable species generated by phosphatase treatment is readily distinguishable from untreated labeled polyphosphate, or labeled nucleotide, then the same would be true of Williams as it has the same structure.

In this regard, we note that *certain aspects* of Williams' invention utilize separation based on charge (FF 13 and 15). Williams also teaches a method wherein "[u]pon incorporation by a polymerase, the dNTP is

hydrolyzed as usual and the liberated pyrophosphate-dye moiety diffuses into the surrounding medium. The free dye molecule is fluorescent and its appearance is imaged at video-rate under a microscope. A flowing stream sweeps the dye away from the parent DNA molecule" (FF 14). Notwithstanding Appellants' contention to the contrary (App. Br. 7 and 9), there is no disclosure of charge separation in this embodiment of Williams' invention. Instead, Williams makes clear that the "free dye molecule is fluorescent and its appearance is imaged at video-rate under a microscope", implying that the liberated pyrophosphate-dye moiety can be distinguished from the labeled nucleotide also present in the solution (FF 14). There is no persuasive argument or evidence on this record to support a contrary conclusion.

Claim 32:

For clarity, we emphasize that claim 32 does not require phosphatase treatment. Appellants contend that "the property/detectability of the label in Williams et al. remains the same before and after the polymerase reaction" (App. Br. 8). In contrast, Appellants contend that in their claim 32, the labeled polyphosphate produced from the polymerase reaction is readily detectable (*id.*). For the reasons set forth above, we are not persuaded. For the same reasons, we are not persuaded by Appellants' contentions regarding the requirement in Williams for a separation by charge of the dye-labeled pyrophosphate product of the polymerase reaction from the dye-labeled nucleotides, prior to detection (*id.*).

CONCLUSION OF LAW

The evidence of record supports the Examiner's finding that Williams anticipates Appellants' claimed invention. The rejection of claims 1 and 32 under 35 U.S.C § 102(b) as being anticipated by Williams is affirmed. Claims 2-7, 9, 11-18, 20-23, 27-31 fall together with claim 1. Claims 33-38, 40, 42-45, and 47-56 fall together with claim 32.

Obviousness:

ISSUE

Did the Examiner err in concluding that Appellants' claimed invention would have been prima facie obvious to a person of ordinary skill in this art in view of the evidence of record?

PRINCIPLES OF LAW

"[T]he [E]xaminer bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). "The '*prima facie* case' serves as a procedural mechanism that shifts the burden of going forward to the applicant, who must produce evidence and/or argument rebutting the case of unpatentability." *Ex parte Frye*, http://www.uspto.gov/ip/boards/bpai/decisions/prec/fd09006013.pdf, slip op. at 8 (BPAI Feb. 26, 2010) (precedential).

> An appellant may attempt to overcome an examiner's obviousness rejection on appeal to the Board by submitting arguments and/or evidence to show that the examiner made an error in either (1) an underlying finding of fact upon which the

> final conclusion of obviousness was based, or (2) the reasoning used to reach the legal conclusion of obviousness. Similarly, the applicant may submit evidence of secondary considerations of non-obviousness.

Id. at 9. "[T]he Board will generally not reach the merits of any issues not contested by an appellant." *Id.* at 10.

ANALYSIS

For each rejection under 35 U.S.C § 103(a) Appellants contend that the secondary reference relied upon by the Examiner fails to make up for the deficiency in Williams discussed above (App. Br. 9-11). For the reasons set forth above, we find no deficiency in the Examiner's reliance on Williams. Accordingly, we are not persuaded by Appellants' contention to the contrary.

CONCLUSION OF LAW

The Examiner did not err in concluding that Appellants' claimed invention would have been prima facie obvious to a person of ordinary skill in this art in view of the evidence of record.

The rejection of claim 8 under 35 U.S.C § 103(a) as unpatentable over the combination of Williams and Wittwer is affirmed. Because the claims were not separately argued claim 39 falls together with claim 8. *See* 37 C.F.R. § 41.37(c)(1)(vii).

The rejection of claim 10 under 35 U.S.C § 103(a) as unpatentable over the combination of Williams and Keller is affirmed. Because the claims were not separately argued claim 41 falls together with claim 10. *See* 37 C.F.R. § 41.37(c)(1)(vii).

The rejection of claim 19 under 35 U.S.C § 103(a) as unpatentable over the combination of Williams and Lichtenwalter is affirmed. Because the claims were not separately argued claim 46 falls together with claim 19. *See* 37 C.F.R. § 41.37(c)(1)(vii).

The rejection of claim 23 under 35 U.S.C § 103(a) as unpatentable over the combination of Williams and Hattori is affirmed. Because the claims were not separately argued claims 24 and 25 fall together with claim 23. *See* 37 C.F.R. § 41.37(c)(1)(vii).

The rejection of claim 25 under 35 U.S.C § 103(a) as unpatentable over the combination of Williams and Bronstein is affirmed. Because the claims were not separately argued claim 26 falls together with claim 25. *See* 37 C.F.R. § 41.37(c)(1)(vii).

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

alw

GE HEALTHCARE BIO-SCIENCES CORP.
PATENT DEPARTMENT
101 CARNEGIE CENTER
PRINCETON, NJ 08540